

Journal

Drugs-Real World Outcomes

Title

Comparison of the Safety of Aspirin Monotherapy and Aspirin and P2Y12 Inhibitor Combination Therapy in Patients Post Coil Embolization during Admission: A Cross-sectional Study Using a Nationwide Inpatients Database

Author

Hiroshi Magara¹, ORCID ID: 0009-0004-8344-4543, E-mail address: y22608@toyaku.ac.jp; Yuri Nakamura¹; Takuaki Tani²; Shinobu Imai²; Anna Kiyomi¹; Kensuke Yoshida¹; Kiyohide Fushimi³; Munetoshi Sugiura^{1*}

Affiliation

¹ Department of Drug safety and Risk Management, School of Pharmacy, Tokyo University of Pharmacy and Life Sciences, 1432-1, Horinouchi, Hachioji, 192-0392, Tokyo, Japan

² Department of Pharmacoepidemiology, Showa University Graduate School of Pharmacy, Tokyo, Japan

³ Department of Health Policy and Informatics, Tokyo Medical and Dental University Graduate School of Medicine, Tokyo, Japan

*Corresponding author

Munetoshi Sugiura, ORCID ID: 0000-0001-5726-0741, E-mail address: msugi@toyaku.ac.jp

Supplementary Information 1. Definition of drugs (Receipt computed code)

Drug	Receipt computed code
Aspirin	610431009, 611140017, 611140019, 611140795, 611140798, 611140849 611140850, 620000484, 620000485, 620000487, 620000488, 620004280 620008577, 620072715, 620072734, 621362001, 621391201, 621391301 610443053, 620000065, 620001952, 620002761, 620006661, 620007816 620009301, 621525202, 621675501, 621676502, 622258001, 622341601 622795301
Ticlopidine	610407355, 610421088, 610461073, 613390007, 620003275, 620003599 620004293, 620004843, 620005039, 620005788, 620005812, 620008315 620008318, 620008330, 620009246, 620814301, 620814502, 620814505 620814506, 620814511, 620814512, 620814521, 620814523, 620814528 620814531, 620814533, 620814534, 620814543, 620814601, 621374002 622738700
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Drug	Receipt computed code
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Antihypertensive drug	610431009, 611140017, 611140795, 611140798, 611140849, 611140850 620000484, 620000485, 620000487, 620000488, 620004280, 620008577 620072715, 620072734, 610406235, 610406281, 610422096, 610454004 610454005, 612170034, 612170100, 612170261, 612170310, 612170363 612170397, 620003614, 620003615, 620003616, 620004669, 620006927 620006928, 620008722, 620008786, 620008891, 620008931, 620309504

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Non-steroidal anti-inflammatory drugs	620000184, 620002040, 620002043, 620002055, 620002057, 620002128 620002131, 620002516, 620002646, 620002647, 620003606, 620003877 620003878, 620003879, 620003880, 620004454, 620004472, 620004621 620004626, 620004716, 620004717, 620004983, 620004984, 620005142 620005144, 620005145, 620005637, 620006095, 620006179, 620006660 620006875, 620006908, 620006978, 620007022, 620007059, 620007088 620007150, 620007151, 620007152, 620007153, 620007159, 620008625 620008632, 620008683, 620008769, 620008780, 620009197, 620094401 620098401, 620098501, 620098702, 620098801, 620098902, 620099003 620099101, 620099201, 620099301, 620099501, 620099601, 620099602 620099701, 620100001, 620100401, 620100501, 620100602, 620100702 620100901, 620107901, 620114004, 621215101, 621215301, 621215401 621215601, 621215602, 621392002, 621534501, 621623201, 621634301 621635802, 621640201, 621640501, 621808201, 622325600, 622709900 622710200, 622710300, 622710400, 640412048, 641140109, 610409337 620006052, 620006053, 620009098, 620009098, 620009098, 620009098 620009098, 620009098, 620009098, 620009098, 620009098, 622400401 622400401, 622400401, 622400401, 622400401, 622400401, 622400401 622400401, 622400401, 622589801, 610406402, 611140098, 611140824 611140828, 620001381, 620001382, 620001383, 620078401, 620078406

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	620008148, 620008149, 620008150, 620008151, 621837703, 621837803

Supplementary information 2. Definition of the Japan Coma Scale

1-digit code	The patient is awake without any stimuli (delirium, confusion, senselessness)
1	Almost fully conscious
2	Unable to recognize time, place, and person
3	Unable to recall name or date of birth
2-digit code	The patient can be aroused with stimuli (stupor, lethargy, hypersomnia, somnolence, drowsiness)
10	By easily by being spoken to (or is responsive with purposeful movements, phrases, or words)
20	With a loud voice or shaking of shoulders (or is almost always responsive to very simple words like yes or no or to movements)
30	Only by repeated mechanical stimuli
3-digit code	The patient cannot be aroused with any forceful mechanical stimuli (deep coma, coma, semicoma)
100	Responds with movements to avoid the stimulus
200	Responds with slight movements, including decerebrate and decorticate posture
300	Does not respond at all except for changes in respiratory rhythm

Supplementary information 3. Definition of ICD-10 codes

Subarachnoid hemorrhage	
I60.0	Subarachnoid hemorrhage from carotid siphon and bifurcation
I60.1	Subarachnoid hemorrhage from middle cerebral artery
I60.2	Subarachnoid hemorrhage from anterior communicating artery
I60.3	Subarachnoid hemorrhage from posterior communicating artery
I60.4	Subarachnoid hemorrhage from basilar artery
I60.5	Subarachnoid hemorrhage from vertebral artery
I60.6	Subarachnoid hemorrhage from other intracranial arteries
I60.7	Subarachnoid hemorrhage from intracranial artery, unspecified
I60.8	Other subarachnoid hemorrhage
I60.9	Subarachnoid hemorrhage, unspecified
Hypertension	
I10	Essential (primary) hypertension
I11	Hypertensive heart disease
I12	Hypertensive renal disease
I13	Hypertensive heart and renal disease
I15	Secondary hypertension
Hyperlipidemia	
E785	Hyperlipidemia unspecified
Diabetes mellitus	
E10	Type 1 diabetes mellitus
E11	Type 2 diabetes mellitus
E12	Malnutrition-related diabetes mellitus
E13	Other specified diabetes mellitus
E14	Unspecified diabetes mellitus
Intracerebral hemorrhage	

Subarachnoid hemorrhage

I61

Intracerebral hemorrhage

Cerebral infarction

I63

Cerebral infarction

Supplementary information 4. Typical dosage of aspirin and P2Y12 inhibitors in Japan

Drugs	Dosing regimen
Aspirin	100 mg/day
Ticlopidine	300 mg/day
Clopidogrel	75 mg/day
Prasugrel	3.75 mg/day

We selected subjects who started antiplatelet therapy within 14 days of subarachnoid hemorrhage onset in this study.

Supplementary information 5. ICD–10 code of bleeding events

Bleeding	Code
Intracranial bleeding	ICD–10: J I60, I61, I62
Gastrointestinal bleeding	ICD–10: K228, K250, K252, K254, K256, K260, K262, K264, K266, K284, K290, K571, K573, K625, K920, K921, K922 Medical procedure codes: D306, D308, D310, D312, D313, J017, K646, K654, K722
Respiratory bleeding	ICD–10: J942, R04
Renal/Urinary tract bleeding	ICD–10: N02, R31

Supplementary information 6. Definition of Glasgow Coma Scale

Japan Coma Scale	Glasgow Coma Scale
0	15
1	15
2	14
3	13
10	12
20	12
30	9
100	7
200	6
300	3

Supplementary information 7. Baseline characteristics of patients in the A and AP groups according to age

	<75 years			≥75 years		
	A group	AP group	p-value	A group	AP group	p-value
	(n=2,044)	(n=1,123)		(n=804)	(n=450)	
Age: mean (SD)	56.9 (11.7)	56.2 (11.6)	0.112	82.3 (5.0)	82.3 (4.9)	0.925
Sex, n (%)			0.030			0.244
Male	761 (37.2)	463 (41.2)		153 (19.0)	73 (16.2)	
Female	1283 (62.8)	660 (58.8)		651 (81.0)	377 (83.8)	
Stent	22 (1.1)	111 (9.9)	<0.001	3 (0.4)	57 (12.7)	<0.001
Location of aneurysms, n (%)						
ICA	544 (26.6)	344 (30.6)	0.018	290 (36.1)	180 (40.0)	0.187
MCA	225 (11.0)	70 (6.2)	<0.001	68 (8.5)	37 (8.2)	0.970
AcomA	532 (26.0)	252 (22.4)	0.028	177 (22.0)	79 (17.6)	0.071
PcomA	31 (1.5)	14 (1.2)	0.648	21 (2.6)	11 (2.4)	1.000
BA	139 (6.8)	97 (8.6)	0.070	56 (7.0)	50 (11.1)	0.015
VA	282 (13.8)	203 (18.1)	0.002	53 (6.6)	37 (8.2)	0.338
Other	342 (16.7)	177 (15.8)	0.512	160 (19.9)	70 (15.6)	0.067
Ambulance use, n (%)	1725 (84.4)	917 (81.7)	0.053	690 (85.8)	380 (84.4)	0.564
Days from onset of SAH to admission, n (%)			0.356			0.946
≤3 days	1954 (95.6)	1082 (96.3)		768(95.5)	431 (95.8)	
4–7 days	90 (4.4)	41 (3.7)		36 (4.5)	19 (4.2)	
ICU admission, n (%)	927 (45.4)	502 (44.7)	0.753	368 (45.8)	202 (44.9)	0.809
Artificial ventilation, n (%)	1266 (61.9)	755 (67.2)	0.003	505 (62.8)	272 (60.4)	0.443
Length of hospital stay, days (SD)	38.2 (32.9)	43.3 (53.7)	0.001	50.4 (48.5)	48.5 (37.0)	0.479
Hospital case volume quartiles, case/4 years, n (%)			0.018			0.764
≤2	129 (6.3)	75 (6.7)		66 (8.2)	34 (7.6)	
3–4	137 (6.7)	88 (7.8)		70 (8.7)	46 (10.2)	
5–11	330 (16.1)	223 (19.9)		162 (20.1)	95 (21.1)	

≥12	1448 (70.8)	737 (65.6)		506 (62.9)	275 (61.1)	
JCS score at admission, n (%)			0.844			0.742
0	506 (24.8)	270 (24.0)		130 (16.2)	75 (16.7)	
1-digit code	561 (27.4)	319 (28.4)		254 (31.6)	142 (31.6)	
2-digit code	436 (21.3)	229 (20.4)		188 (23.4)	94 (20.9)	
3-digit code	541 (26.5)	305 (27.2)		232 (28.9)	139 (30.9)	
GCS			0.224			0.285
15	543 (26.6)	286 (25.5)		239 (29.7)	121 (26.9)	
14	110 (5.4)	43 (3.8)		72 (9.0)	31 (6.9)	
13	103 (5.0)	68 (6.1)		68 (8.5)	32 (7.1)	
12-7	854 (41.8)	478 (42.6)		244 (30.3)	154 (34.2)	
6-3	434 (21.2)	248 (22.1)		181 (22.5)	112 (24.9)	
mRS score at admission, n (%)			0.547			0.015
0	1579 (77.3)	877 (78.1)		461 (57.3)	238 (52.9)	
1	219 (10.7)	133 (11.8)		134 (16.7)	111 (24.7)	
2	75 (3.7)	33 (2.9)		63 (7.8)	34 (7.6)	
3	32 (1.6)	16 (1.4)		62 (7.7)	25 (5.6)	
4	62 (3.0)	25 (2.2)		37 (4.6)	23 (5.1)	
5	77 (3.8)	39 (3.5)		47 (5.8)	19 (4.2)	
Charlson Comorbidity Index, n (%)			0.421			0.682
0	1267 (62.0)	679 (60.5)		441 (54.9)	253 (56.2)	
≥1	777 (38.0)	444 (39.5)		363 (45.1)	197 (43.8)	
Comorbidities, n (%)						
Hypertension	1146 (56.1)	614 (54.7)	0.474	481 (59.8)	260 (57.8)	0.517
Diabetes	156 (7.6)	90 (8.0)	0.753	116 (14.4)	60 (13.3)	0.652
Hyperlipidemia	238 (11.6)	123 (11.0)	0.598	98 (12.2)	50 (11.1)	0.634
Cerebral infarction	187 (9.1)	149 (13.3)	<0.001	66 (8.2)	36 (8.0)	0.982
Cerebral hemorrhage	59 (2.9)	24 (2.1)	0.252	39 (4.9)	12 (2.7)	0.084
Concomitant medication, n (%)						
Fasudil	1723 (84.3)	886 (78.9)	<0.001	628 (78.1)	357 (79.3)	0.664

Ozagrel	820 (40.1)	463 (41.2)	0.568	264 (32.8)	171 (38.0)	0.075
Cilostazol	780 (38.2)	401 (35.7)	0.185	257 (32.0)	149 (33.1)	0.724
Statins	731 (35.8)	355 (31.6)	0.021	289 (35.9)	168 (37.3)	0.668
Edaravone	591 (28.9)	406 (36.2)	<0.001	190 (23.6)	139 (30.9)	0.006
EPA	103 (5.0)	50 (4.5)	0.516	33 (4.1)	22 (4.9)	0.612
Anticoagulant	65 (3.2)	53 (4.7)	0.037	90 (11.2)	50 (11.1)	1.000
NSAIDs	1447 (70.8)	768 (68.4)	0.170	403 (50.1)	214 (47.6)	0.416

A group: aspirin monotherapy, AP group: combination of aspirin and P2Y12 inhibitor

AcomA: anterior communicating artery, BA: basilar artery, EPA: eicosapentaenoic acid, GCS: Glasgow Coma Scale, ICA: internal carotid artery, ICU: intensive care unit, JCS: Japan Coma Scale, MCA: middle cerebral artery, mRS: modified Rankin Scale, NSAIDs: non-steroidal anti-inflammatory drugs, PcomA: posterior communicating artery, SD: standard deviation, VA: vertebral artery.

Concomitant medications: All medications were administered during hospitalization.

Supplementary information 8. Baseline characteristics of patients in the A and AP groups according to concomitant cilostazol use

	Concomitant cilostazol use			Non-concomitant cilostazol use		
	A group (n=1,037)	AP group (n=550)	p-value	A group (n=1,811)	AP group (n=1,023)	p-value
Age: mean (SD)	63.2 (15.0)	63.0 (15.5)	0.759	64.5 (15.6)	64.0 (15.6)	0.419
Age, n (%)			0.346			0.694
<75 years	780 (75.2)	401 (72.9)		1264 (69.8)	722 (70.6)	
≥75 years	257 (24.8)	149 (27.1)		547 (30.2)	301 (29.4)	
Sex, n (%)			0.343			0.381
Male	1518 (30.1)	951 (29.6)		589 (32.5)	350 (34.2)	
Female	712 (68.7)	364 (66.2)		1222 (67.5)	673 (65.8)	
Stent	18 (1.7)	46 (8.4)	<0.001	7 (0.4)	122 (11.9)	<0.001
Location of aneurysms, n (%)						
ICA	309 (29.8)	190 (34.5)	0.060	525 (29.0)	334 (32.6)	0.046
MCA	102 (9.8)	43 (7.8)	0.216	191 (10.5)	64 (6.3)	<0.001
AcomA	260 (25.1)	128 (23.3)	0.464	449 (24.8)	203 (19.8)	0.003
PcomA	29 (2.8)	8 (1.5)	0.131	23 (1.3)	17 (1.7)	0.494
BA	77 (7.4)	48 (8.7)	0.413	118 (6.5)	99 (9.7)	0.003
VA	110 (10.6)	73 (13.3)	0.134	225 (12.4)	167 (16.3)	0.005
Other	166 (16.0)	76 (13.8)	0.280	336 (18.6)	171 (16.7)	0.240
Ambulance use, n (%)	916 (88.3)	471 (85.6)	0.144	1499 (82.8)	826 (80.7)	0.193
Days from onset of SAH to admission, n (%)			0.915			0.352
≤3 days	991 (95.6)	527 (95.8)		1731 (95.6)	986 (96.4)	
4–7 days	46 (4.4)	23 (4.2)		80 (4.4)	37 (3.6)	
ICU admission, n (%)	467 (45.0)	233 (42.4)	0.334	828 (45.7)	471 (46.0)	0.900
Artificial ventilation, n (%)	694 (66.9)	345 (62.7)	0.106	1077 (59.5)	682 (66.7)	<0.001

Length of hospital stay, days (SD)	44.5 (31.1)	51.3 (65.4)	0.005	40.0 (41.8)	41.3 (38.0)	0.414
Hospital case volume quartiles, case/4 years, n (%)			0.396			0.002
≤2	72 (6.9)	38 (6.9)		123 (6.8)	71 (6.9)	
3–4	101 (9.7)	44 (8.0)		106 (5.9)	90 (8.8)	
5–11	177 (17.1)	110 (20.0)		315 (17.4)	208 (20.3)	
≥12	687 (66.2)	358 (65.1)		1267 (70.0)	654 (63.9)	
JCS score at admission, n (%)			0.004			0.047
0	215 (20.7)	114 (20.7)		421 (23.2)	231 (22.6)	
1–digit code	273 (26.3)	190 (34.5)		542 (29.9)	271 (26.5)	
2–digit code	243 (23.4)	113 (20.5)		381 (21.0)	210 (20.5)	
3–digit code	306 (29.5)	133 (24.2)		467 (25.8)	311 (30.4)	
GCS			0.013			0.009
15	373 (36.0)	226 (41.1)		476 (26.3)	272 (26.6)	
14	55 (5.3)	46 (8.4)		122 (6.7)	42 (4.1)	
13	60 (5.8)	32 (5.8)		116 (6.4)	54 (5.3)	
12–7	306 (29.5)	135 (24.5)		725 (40.0)	406 (39.7)	
6–3	243 (23.4)	111 (20.2)		372 (20.5)	249 (24.3)	
mRS score at admission, n (%)			0.080			0.375
0	773 (74.5)	392 (71.3)		1267 (70.0)	723 (70.7)	
1	118 (11.4)	91 (16.5)		235 (13.0)	153 (15.0)	
2	38 (3.7)	20 (3.6)		100 (5.5)	47 (4.6)	
3	30 (2.9)	11 (2.0)		64 (3.5)	30 (2.9)	
4	40 (3.9)	16 (2.9)		59 (3.3)	32 (3.1)	
5	38 (3.7)	20 (3.6)		86 (4.7)	38 (3.7)	
Charlson Comorbidity Index, n (%)			0.493			1.000
0	655 (63.2)	337 (61.3)		1053 (58.1)	595 (58.2)	
≥1	382 (36.8)	213 (38.7)		758 (41.9)	428 (41.8)	
Comorbidities, n (%)						
Hypertension	578 (55.7)	301 (54.7)	0.740	1049 (57.9)	573 (56.0)	0.343
Diabetes	90 (8.7)	56 (10.2)	0.371	182 (10.0)	94 (9.2)	0.499
Hyperlipidemia	146 (14.1)	67 (12.2)	0.328	190 (10.5)	106 (10.4)	0.964

Cerebral infarction	122 (11.8)	71 (12.9)	0.560	131 (7.2)	114 (11.1)	<0.001
Cerebral hemorrhage	32 (3.1)	8 (1.5)	0.071	66 (3.6)	28 (2.7)	0.236
Concomitant medication, n (%)						
Fasudil	945 (91.1)	494 (89.8)	0.445	1406 (77.6)	749 (73.2)	0.009
Ozagrel	427 (41.2)	230 (41.8)	0.847	657 (36.3)	404 (39.5)	0.097
Statins	496 (47.8)	237 (43.1)	0.080	524 (28.9)	286 (28.0)	0.610
Edaravone	395 (38.1)	221 (40.2)	0.448	386 (21.3)	324 (31.7)	<0.001
EPA	89 (8.6)	48 (8.7)	0.997	47 (2.6)	24 (2.3)	0.778
Anticoagulant	67 (6.5)	50 (9.1)	0.071	88 (4.9)	53 (5.2)	0.773
NSAIDs	761 (73.4)	394 (71.6)	0.493	1089 (60.1)	588 (57.5)	0.180

A group: aspirin monotherapy, AP group: combination of aspirin and P2Y12 inhibitor

AcomA: anterior communicating artery, BA: basilar artery, EPA: eicosapentaenoic acid, GCS: Glasgow Coma Scale, ICA: internal carotid artery, ICU: intensive care unit, JCS: Japan Coma Scale, MCA: middle cerebral artery, mRS: modified Rankin Scale, NSAIDs: non-steroidal anti-inflammatory drugs, PcomA: posterior communicating artery, SD: standard deviation, VA: vertebral artery.

Concomitant medications: All medications were administered during hospitalization.